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10/539,450	12/23/2005	Hisashi Narimatsu	GRT/159-90	6812

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EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	PAPER NUMBER
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/539,450	NARIMATSU ET AL.
	Examiner	Art Unit
	Ganapathirama Raghu	1652

TH

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) *31-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

In response to the Office Action mailed on 11/17/2006, applicants' filed a response and amendment received on 03/19/2007. Said amendment, canceled claims 1-20 and added new claims 21-40. Thus new claims 21-40 are pending in this application. Claims 31-40 are withdrawn as they are non-elected inventions and belong to newly added group of process claims, as the original election to restriction requirement was directed to polypeptide (Group I, claims 1-6, letter dated 09/22/06). Newly submitted claims 31-40 are directed to an invention that is independent or distinct from the invention originally elected for the following reasons:

Inventions of claims 21-30 and Inventions of claims 31-40 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case claims 31-40 are directed to a process of using the elected polypeptide, said polypeptide can be used in a materially different process such as antigen for raising antibodies as opposed to its use in a process encompassed in claims 31-40. Accordingly, claims 31-40 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Therefore, new claims 21-30, directed to polypeptides are now under consideration.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Withdrawn- Claim Rejections 35 USC § 101

Previous rejection of claims 1-6, under 35 U.S.C. 101 is withdrawn in view of the applicants' amendments and cancellation of claims.

Withdrawn- Claim Rejections 35 USC § 112

Previous rejection of claims 2 and 6, under 35 U.S.C. 112 second paragraph is withdrawn in view of the applicants' amendments and cancellation of claims.

Previous rejection of claims 1-3, under 35 U.S.C. 112 first paragraph for written description is withdrawn in view of the applicants' amendments and cancellation of claims.

Withdrawn- Claim Rejections 35 USC § 102

Previous rejection of claims 1-6, rejected under 35 U.S.C. 102(b) as being anticipated by Strausberg et al., (PNAS., 2002, Vol. 99 (26): 16899-16903), is withdrawn due to applicants' amendments to the claims and cancellation of claims.

Previous rejection of claims 1-3 and 6 rejected under 35 U.S.C. 102(b) as being anticipated by Kawai et al., (Nature, 2001, Vol. 409: 685-690), is withdrawn due to applicants' amendments to the claims and cancellation of claims.

Claim Objections

Claims 28 and 29 are objected to because of the following informalities:

Applicant is advised that should claim 28 be found allowable, claim 29 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Maintained- Claim Rejections 35 USC § 112

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 24, 26 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics and comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and encoded by polynucleotides of SEQ ID NOs: 1 and 3 respectively, does not reasonably provide enablement for any isolated β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics and comprising an amino acid sequence having 90% sequence identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 21, 24, 26 and 28-30 are so broad as to encompass for any isolated β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics

and comprising an amino acid sequence having 90% sequence identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides and encoding polynucleotides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to an isolated β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics and comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and encoded by polynucleotides of SEQ ID NOs: 1 and 3 respectively, but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides and encoding polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claim, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompass all modifications to any isolated β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics and comprising an amino acid sequence having 90% sequence identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and having said specific activity and biochemical characteristics, because the specification does not establish: (A) regions of the protein/polynucleotide structure which may be modified without affecting the activity of encoded β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics; (B) the general tolerance of the polypeptide and the polynucleotide encoding β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claim broadly including polynucleotides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any isolated β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics and comprising an amino acid sequence having 90% sequence identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' have traversed this rejection asking for an explanation for the basis of rejection and the claimed invention is enabled if any person skilled in the art can make and use the invention without undue experimentation and need only routine experimentation. Applicants' arguments have been considered and found to be non-persuasive for the following reasons and the scientific body of work presented below supports the basis of rejection.

While methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc., are well known to the skilled artisan, producing variants with 90% sequence identity to SEQ ID NO: 2 or 4 with β1,3-N-acetyl-D-galactosamine transferase activity, requires that one of ordinary skill in the art know or be provided with guidance for the selection of which, of the infinite number of variants, have the activity. Without such guidance, one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims, this would clearly constitute

undue experimentation. Guo et al., (PNAS, 2004, Vol. 101 (25): 9205-9210) teach that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (p 9206, paragraph 4). Guo et al., (*supra*) further show that the percentage of active mutants for multiple mutations appears to be exponentially related to this by the simple formula $(.66)^{X}$ X 100% where **x** is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, 90% identity allows up to 50 mutations within the 500 and 504 amino acids of SEQ ID NOs: 2 and 4 respectively and, thus, only $(0.66)^{50}$ X 100% or 9.5 x 10^{-8} % of random mutants having 90% identity would be active Current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would allow for finding a reasonable number of active mutants within hundred thousand inactive mutants (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish). But finding a few mutants within several million or more, as in the claims to 90% identity, would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Applying this estimate to the instant protein, a functional equivalent thereof with 90% sequence identity to SEQ ID NOs: 2 or 4, as recited in claims 21 and 24-30, an extremely low number of active mutants will be present among an enormously large number of inactive mutants

and as such screening for these active mutants would be burdensome and undue experimentation when there is no guidance provided in the specification.

Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strausberg et al., (PNAS., 2002, Vol. 99 (26): 16899-16903) or Kawai et al., (Nature, 2001, Vol. 409: 685-690), in view of Wandall et al., (JBC., 1997, Vol. 272 (38): 23503-23514). Claims 21-30 are directed to any isolated β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics and comprising an amino acid sequence having 90% sequence identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and encoded by a nucleotide sequence that can hybridize under defined high stringent conditions to the complement of SEQ ID NO: 1 or 3. Strausberg et al., (*supra*) teach the isolation of a polypeptide (B3 GALNT2; ORF Name= RP4-534P7.1-001) annotated as β1,3-N-acetyl-D- galactosamine transferase that has 100% sequence homology to SEQ ID NO: 2 or to a polypeptide having an amino acid sequence covering amino acids 189 to 500 of SEQ ID NO: 2 or to a polypeptide having an amino acid sequence covering amino acids 36 to 500 of SEQ ID NO: 2 of the instant application. Kawai et al., (*supra*) teach the isolation of a polypeptide (for clone identity http://genomec.gsc.riken.go.jp/genome/fantom1/fig./nature/supplement/;user name: fantom1; password:fntm0828) annotated as β1,3-N-acetyl-D- galactosamine transferase that has 100%

sequence homology to SEQ ID NO: 4 or to a polypeptide having an amino acid sequence covering amino acids 35 to 504 of SEQ ID NO: 4 of the instant application. Both the cited references are silent regarding pH and divalent cation requirement for the specific activity of isolated polypeptide. Wandall et al., teach the isolation, expression and biochemical characterization of three members of human N-Acetylgalactosaminyltransferases, optimal pH range and requirement of divalent cations like Mn^{2+} for the activity of said enzymes. Note Wandall et al., assayed all three human N-Acetylgalactosaminyltransferases in a buffer comprising 10 mM $MnCl_2$ at pH 7.4. Therefore, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Strausberg et al., or Kawai et al., and Wandall et al., to express the cDNA encoding the polypeptides as taught by Strausberg et al., or Kawai et al., and to reconstitute the expressed polypeptides in a buffer system as disclosed by Wandall et al., for the assay of the enzymatic activity of human N-Acetylgalactosaminyltransferases enzymes. Motivation to combine the teachings derives from the fact β1,3-N-acetyl-D- galactosamine transferases are employed in industrial applications for their ability to synthesize various sugar molecules and modification of proteins by their ability to transfer sugar moieties on acceptor sites of said proteins. The expectation of success is high, because, the disclosure of Strausberg et al., or Kawai et al., of cloning of a gene encoding a polypeptide annotated as β1,3-N-acetyl-D- galactosamine transferase and the teachings of Wandall et al., disclosing the suitable expression vectors and determination of optimal activity and stability conditions for the isolated polypeptide. Therefore, claims 21-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strausberg et al., (PNAS., 2002, Vol. 99 (26):

16899-16903) or Kawai et al., (Nature, 2001, Vol. 409: 685-690), in view of Wandall et al., (JBC., 1997, Vol. 272 (38): 23503-23514).

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1) Claims 31-40 are withdrawn as they are non-elected inventions.

2) Claims 28 and 29 are objected to because of informalities.

3) Claims 21, 24, 26 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, for enablement.

4) Claims 21-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strausberg et al., (PNAS., 2002, Vol. 99 (26): 16899-16903) or Kawai et al., (Nature, 2001, Vol. 409: 685-690), in view of Wandall et al., (JBC., 1997, Vol. 272 (38): 23503-23514).

Conclusion

None of the claims are allowable. Claims 21-30 are rejected/objected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 01, 2007.

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